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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/727,311	11/29/2000	William D. Huse	P-IX 4526	3119
23601	7590	03/15/2004	EXAMINER	
CAMPBELL & FLORES LLP 4370 LA JOLLA VILLAGE DRIVE 7TH FLOOR SAN DIEGO, CA 92122			LAMBERTSON, DAVID A	
			ART UNIT	PAPER NUMBER
			1636	

DATE MAILED: 03/15/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

**Advisory Action**

Application No.

09/727,311

Applicant(s)

HUSE, WILLIAM D.

Examiner

David A. Lambertson

Art Unit

1636

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 11 February 2004 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE. Therefore, further action by the applicant is required to avoid abandonment of this application. A proper reply to a final rejection under 37 CFR 1.113 may only be either: (1) a timely filed amendment which places the application in condition for allowance; (2) a timely filed Notice of Appeal (with appeal fee); or (3) a timely filed Request for Continued Examination (RCE) in compliance with 37 CFR 1.114.

**PERIOD FOR REPLY** [check either a) or b)]

- a) ☐ The period for reply expires \_\_\_\_\_ months from the mailing date of the final rejection.
- b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.
- ONLY CHECK THIS BOX WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

1. ☒ A Notice of Appeal was filed on 11 February 2004. Appellant's Brief must be filed within the period set forth in 37 CFR 1.192(a), or any extension thereof (37 CFR 1.191(d)), to avoid dismissal of the appeal.
2. ☐ The proposed amendment(s) will not be entered because:
- (a) ☐ they raise new issues that would require further consideration and/or search (see NOTE below);
- (b) ☐ they raise the issue of new matter (see Note below);
- (c) ☐ they are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
- (d) ☐ they present additional claims without canceling a corresponding number of finally rejected claims.

NOTE: \_\_\_\_\_

3. ☐ Applicant's reply has overcome the following rejection(s): \_\_\_\_\_.
4. ☐ Newly proposed or amended claim(s) \_\_\_\_\_ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).
5. ☒ The a) ☐ affidavit, b) ☐ exhibit, or c) ☒ request for reconsideration has been considered but does NOT place the application in condition for allowance because: See Continuation Sheet.
6. ☐ The affidavit or exhibit will NOT be considered because it is not directed SOLELY to issues which were newly raised by the Examiner in the final rejection.
7. ☒ For purposes of Appeal, the proposed amendment(s) a) ☐ will not be entered or b) ☒ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.

The status of the claim(s) is (or will be) as follows:

Claim(s) allowed: \_\_\_\_\_

Claim(s) objected to: \_\_\_\_\_

Claim(s) rejected: 1 and 88-91.

Claim(s) withdrawn from consideration: \_\_\_\_\_

8. ☐ The drawing correction filed on \_\_\_\_\_ is a) ☐ approved or b) ☐ disapproved by the Examiner.
9. ☐ Note the attached Information Disclosure Statement(s) (PTO-1449) Paper No(s). \_\_\_\_\_
10. ☐ Other: \_\_\_\_\_

Continuation of 5. does NOT place the application in condition for allowance because: Applicant's arguments are not persuasive with regard to the rejections under 35 USC § 102(e). Although all of Applicant's arguments have been addressed previously, the arguments will be clarified in a point-by-point manner with respect to Applicant's arguments. Applicant makes the following arguments:

1. Applicant reiterates that the Ladner '063 application is not enabled as of the priority date of the application (see page 2, paragraphs 2-3 of Applicant's response).
2. Applicant suggests that forethought to potential problems is insufficient to satisfy the enablement requirement (see page 3, paragraph 3 of Applicant's response).
3. Applicant reiterates that the argument is that the '063 Ladner application lacks sufficient guidance as to whether any signal sequence would function in the described invention. Applicant then appears to argue that the alleged contradictory results with the Gene VIII putative signal sequence is sufficient to void any demonstration of success with a different signal sequence (see page 4, paragraph 1 of Applicant's response).
4. Applicant asserts that, with respect to the results obtained with the phoA signal sequence, that the Office fails to provide any reason why a person skilled in the art would choose to select any single embodiment of the invention over another. In other words, Applicant calls into question why one of skill in the art would choose to follow the successful teachings of using the phoA signal sequence, as opposed to the alleged unsuccessful demonstration using the putative Gene VIII signal sequence (see page 4, paragraph 3 of Applicant's response).
5. Applicant purports that the Office fails to address the issue of non-enablement because the issue of speculation regarding which signal sequences to use is not clearly addressed (see page 5, paragraphs 1-3 of Applicant's response).
6. Applicant contends that the Office's opinion that the '063 application serves as having sufficient guidance on the use of different signal sequences because it suggests the substitution of different signal sequences for the putative Gene VIII signal sequence evades the issue of "sufficient guidance" (see page 6, paragraph 1 of Applicant's response).
7. Applicant asserts that the totality of the '063 is nothing more than an invitation to experimentation, and that the Office has misplaced its reliance on the enablement of the phoA signal sequence in a display of biased hindsight (see page 6, paragraph 2 of Applicant's response).
8. Applicant maintains their position that the Markland reference raises serious doubts as to the enablement of the '063 application because, in their opinion, the results as reported do not correlate with the teachings of the '063 application (see page 7-8 of Applicant's response).

Applicant's arguments have been fully considered, but are not convincing for the following reasons:

1. As stated in the previous FINAL Office Action, there was no enablement rejection present in the '063 application, indicating that the Office did not determine the application to be non-enabling. Furthermore, Applicant has failed to provide evidence that the art of making fusion proteins with heterologous signal sequences is unpredictable in any way. Applicant simply provides their opinion that it would be unpredictable, and therefore non-enabled in the context of the '063 application. However, the state of the art of making fusion proteins with heterologous signal sequences at the time of the '063 application was highly routine. For example, Michaelis et al. (J. of Bacteriol. 154: 356-365, 1983), Bassford et al. (J. of Bacteriol. 139: 19-31, 1979), and Takahara et al. (J. of Biol. Chem. 260: 2670-2674, 1985) all demonstrated the successful use of gene fusions with heterologous signal sequences. Therefore, the skilled artisan would recognize that it was routine experimentation to substitute any signal sequence for the Gene VIII "putative" signal sequence, and that there would be a reasonable expectation of success in doing so. This is further evident from the fact that Ladner anticipates and suggests doing so; with this suggestion, it is clear that Ladner predicted the substitution of any signal sequence in their invention. As such, it is not persuasive that such substitutions would amount to anything that is unpredictable.
2. It is not simply the forethought that additional signal sequences could be used in the invention described in the '063 Ladner application. It is the combination of that forethought (the predictability and amount of experimentation), combined with the teachings in the state of the art (see above, where the Office provides evidence with regard to the routine practice of using any heterologous signal sequence to make a fusion protein), and the guidance in the specification that a particular embodiment (the use of the phoA signal sequence) that satisfies the enablement of the '063 application. It is improper not to consider all of the relevant Wands factors when establishing the non-enablement of a reference.
3. The Office does not agree that there is a lack of guidance in the '063 Ladner application regarding the use of any signal sequence. Again, the '063 application clearly suggests the use of any other signal sequence, many of which were well known in the art at the time of the '063 application. Indeed, the '063 successfully demonstrates the use of such a different sequence (i.e., the phoA sequence). Furthermore, there is no clear reason as to why one would dismiss the successful teachings of using the phoA sequence simply because the "putative" Gene VIII signal sequence did not work. On the other hand, because the Gene VIII was disclosed in the specification as "putative," one would predict that it might not work, and thus would predict the need to use a more well-defined signal sequence in its

place. The fact that Ladner predicts and suggests doing this is indeed sufficient guidance. This is especially true when coupled to the fact that a working example of this guidance is set forth in the '063 application (i.e., the ability of the phoA sequence to successfully target heterologous sequences for surface expression).

4. There is adequate reason to give weight to the phoA sequence, in direct contrast to Applicant's assertion. Specifically, the particular example cited by the Office actually worked, and one of skill in the art would certainly not ignore a working example. This is especially true in this instance because, while Applicant chooses to focus on a single contradictory example (i.e., the Gene VIII signal sequence), the specification clearly identified that the particular sequence might be a problem because it was only a "putative" signal sequence, and had not actually been characterized as a signal sequence. Significantly, Applicant has not provided any rationale as to why one of skill in the art would absolutely ignore the successful teaching of using the phoA sequence. Notably, this single embodiment is sufficient to anticipate the instant claims because it is a species within the claimed genus. Therefore, the reference is anticipatory because it teaches the single working example, at the very least.

5. The Office has not failed to address the issue of non-enablement. Rather, it is the Applicant who has failed to adequately show that the specification is not enabled. Even if, *arguendo*, the claims are not enabled for the broad scope in which they are later claimed by Ladner, they are enabled for the specific embodiment of using the phoA signal sequence. This single example, in and of itself, teaches a specific embodiment of the invention that is claimed by applicant, which is therefore anticipatory. Applicant has failed to show any evidence that the phoA signal sequence did not work in the '063 application. Applicant has simply opined that because the Gene VIII signal sequence did not work, one of skill in the art would doubt the veracity of another example.

6. Again, the Office has shown that the '063 application provides sufficient guidance regarding the use of the phoA signal to cause the surface expression of a heterologous protein. This single working example is sufficient to anticipate the instant claims because it is a species within the scope of the claimed invention. There is no evidence teaching away from the use of the phoA signal sequence, thus there is no reason to dismiss this result. Furthermore, the '063 application anticipates the potential problems with the "putative" Gene VIII signal sequence and suggests using other known signal sequences (going so far as to demonstrate the use of the phoA sequence); this is sufficient guidance, given the state of the prior art regarding the description and use of heterologous signal sequences to direct the expression of fusion proteins to the cell surface (again, see Michaelis et al. (J. of Bacteriol. 154: 356-365, 1983), Bassford et al. (J. of Bacteriol. 139: 19-31, 1979), and Takahara et al. (J. of Biol. Chem. 260: 2670-2674, 1985)).

7. The Office's reliance on the phoA example is not misplaced or biased. It is simply a teaching that anticipates the instantly claimed invention. Applicant has provided no evidence to suggest that this teaching should be ignored. Applicant has simply relied on the alleged non-enablement of the use of the Gene VIII sequence in an attempt to dismiss the actual working example of the phoA sequence. The Office cannot simply ignore a working embodiment of an invention at the behest of Applicant. Furthermore, there is no invitation to experiment with regard to the phoA signal sequence; the '063 clearly teaches that this embodiment works. With regard to an invitation to experiment concerning the use of other signal sequences, when considering the state of the art, one of skill would understand that a number of signal sequences were known in the art, and that these sequences had been used to target heterologous peptide fusion to the cell surface. Therefore, any experimentation with regard to substituting one of these sequences for the phoA sequence would be no more than a routine process, with a high expectation of success.

8. The Office fails to see how the Markland reference provides any contradictory evidence to the use of the phoA signal sequence for the heterologous expression of peptides on the cell surface. In the '063 application, it is indicated that the phoA signal sequence adequately targets the BPTI/VIII coat fusion protein to the cell surface. The Markland reference also shows this in Figure 2, lanes 12 and 13, where a 12 kDa species indicating a processed species is clearly evident (see also page 15, right column, third full paragraph). This actually supports the findings in the '063 application, in contrast to Applicant's position that it calls into question the teachings.

In conclusion, and as stated before in the previous Office Action, the '063 application is not found to be non-enabling, thus the priority date for the rejection under 35 USC 102(e) is determined to be accurate. The '063 application provides a working example of a specific embodiment of the instantly claimed invention, wherein the phoA signal sequence is used to target a heterologous peptide to the cell surface. Furthermore, the specification, when interpreted in view of the state of the art at the time of the invention, provided sufficient guidance regarding the substitution of any known signal sequence into the invention. As such, Applicant's allegation that the '063 application does not provide an enabled disclosure is not found convincing, and the rejection is maintained.

Regarding Applicant's traversal of the rejection under Obviousness-Type Double Patenting, Applicant provides the following arguments:

1. Applicant asserts that claim 1 of the '530 patent is directed to "particular and distinct modes of expression," and is therefore not obvious in view of instant claim 1.

2. Applicant asserts that claim 29 "is not directed to a desirable bias of random codon sequences."

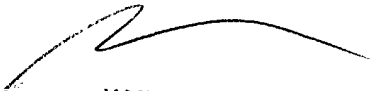
Applicant's arguments are not convincing for the following reasons:

1. The fact that claim 1 of the '530 patent is directed to "particular and distinct modes of expression" is the reason why the instant claim is obvious. The specific embodiment of claim 1 of the '530 patent falls within the limitations of instant claim 1, therefore anticipating claim 1. Therefore, because the specific embodiment anticipates a genus claim, that genus claim is necessarily obvious in light of the

specific embodiment that falls within its scope.

2. It is indeed true that claim 29 "is not directed to a desirable bias of random codon sequences." That is why claim 29 is broader in scope than claim 1 of the instant application. However, one of skill in the art would read the specification and understand that a preferred embodiment of the invention involves the use of a desirable bias of random codon sequences, as the specification clearly indicates this (see entire document, for example column 2, lines 22-27; column 5, lines 10-24; etc.). Thus, because claim 1 is a preferred embodiment of claim 29, set forth as such in the specification of the '530 patent, it would be obvious for one of skill in the art to make the invention claimed in the instant claim 1.

Because of the reasons set forth above, the indicated claims are still found to be obvious in view of the '530 patent.



JAMES KETTER  
PRIMARY EXAMINER